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Two years outcome of isolated distal deep vein thrombosis

Michelangelo Sartori *, Ludovica Migliaccio, Elisabetta Favaretto, Gualtiero Palareti, Benilde Cosmi

Department of Angiology and Blood Coagulation "Marino Golinelli", S. Orsola-Malpighi University Hospital, 40138 Bologna, Italy

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ABSTRACT

Background: Isolated distal deep vein thrombosis (IDDVT) is frequently found in symptomatic outpatients, but its long term outcome is still uncertain.
Aims: To assess IDDVT long term outcome and the impact of IDDVT characteristics on outcome.
Methods: In a prospective, single center study we enrolled symptomatic outpatients in whom IDDVT was detected by whole-leg compression ultrasonography. Patients with provoked IDDVT were treated with low molecular weight heparins (LMWH) for 30 days while those with unprovoked IDDVT received with vitamin K antagonists (VKA) for three months. The primary end-point was the rate of the composite of pulmonary embolism (PE), proximal deep vein thrombosis (DVT), and IDDVT recurrence/extension during 24 month follow-up.
Results: 90 patients (age 61 ± 18, male 48.9%) were enrolled. Risk factors for thrombosis were reduced mobility (34.4%), obesity (25.3%), surgery (15.6%), and previous DVT (15.6%) and cancer in 8 patients (8.9%). Eighty-eight patients were treated (56 with LMWH and 32 with VKA). During follow-up (median 24 ± 2 months), 17 events were recorded, which included 3 PE (two in cancer patients), 4 proximal DVTs (one in cancer patient) and 10 IDDVT. Male sex (HR 4.73 CI95%: 1.55-14.5; p = 0.006) and cancer (HR 5.47 CI95%: 1.76-17.6; p = 0.003) were associated with a higher risk of complications, whereas IDDVT anatomical characteristics, anticoagulant therapy type, and provoked IDDVT were not.
Conclusions: The risk of recurrent venous thromboembolism after IDDVT may be relevant in male patients or in patients with active cancer. Larger studies are needed to address this issue.

Introduction

Thromboses that are confined to the infra-popliteal deep veins of the lower limbs (isolated distal deep vein thrombosis, IDDVT) are a frequent finding in symptomatic outpatients [1] and seem to be associated with a lower risk of recurrence than proximal deep vein thrombosis (DVT) [2,3]. Galanaud et coll. reported lower rates of major bleeding, recurrent venous thrombo-embolism (VTE) and death in patients with IDDVT than in those with proximal DVT during the acute phase of thrombosis [4]. A recent patient-level meta-analysis showed that patients with proximal DVT had a more than 4-fold higher cumulative rate of recurrent VTE compared with patients with IDDVT [5], the risk being 1.0 per 100 pt-years [5]. However in the medical records of residents of the Worcester (MA), the rates of VTE recurrence and pulmonary embolism (PE) did not differ significantly between patients with IDDVT and proximal DVT at 6 months [6]. Moreover, Gillet et al. showed that PE is not rare in the natural history of muscular calf vein thrombosis and during a follow-up of 26.7 months, 18.8% of patients had at least one VTE recurrence [7]. Twenty-nine years ago a randomised study on oral anticoagulation in patients with IDDVT showed that almost all the patients randomized to warfarin did not have recurrent VTE, whereas 19 of 28 patients that did not received warfarin had recurrent VTE [8]. Since the natural history of IDDVT is still uncertain and the factors associated with VTE recurrence are unclear, the purpose of this study was to assess the long term outcome of IDDVT and ascertain the impact of IDDVT features on the risk of thromboembolic complications.

Methods

Study Design

Patients were enrolled from September 2009 to January 2011 in a tertiary care teaching hospital (S. Orsola-Malpighi University Hospital, Bologna, Italy), as previously described [9]. Briefly, symptomatic outpatients referred by general practitioners or the emergency department to the vascular emergency room for suspected acute DVT of the lower limbs underwent: a) D-dimer testing; b) whole-leg compression ultrasonography of both lower limbs. A personal and family history was elicited from each patient by the physician in charge who also performed a physical examination. Patients with IDDVT were enrolled,

* Corresponding author at: U.O. di Angiologia e Malattie della Coagulazione "Marino Golinelli", Azienda Ospedaliera di Bologna, Policlinico Sant'Orsola Malpighi, Pad. 2, Via Albertoni, 15 40138 Bologna. Tel.: +39 051 6362482; fax: +39 051 636 2517.
E-mail address: michelangelo.sartori@aosp.bo.it (M. Sartori).

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whereas patients with proximal DVT were excluded from the study. Moreover, patients were excluded if younger than 18 years, if they had renal insufficiency (GFR < 30 ml/min), if they were receiving vitamin K antagonists (VKA), or low-molecular -weight heparin (LMWH) or fondaparinux for more than 24 h, pregnant or in puerperium, if they had concomitant PE.

It was not possible to enroll all consecutive eligible patients but the first eligible patient of each day was included, to minimize selection bias. The enrollment was performed during business days. The design of the study was prospective: the study started when IDDVT was diagnosed and the patients followed in our outpatient service. The physician in charge decided treatment type on the basis of the absence (unprovoked IDDVT) or presence of established transient risk factors for VTE, such as trauma, lower limb immobilization, surgery, hormonal therapy which defined provoked IDDVT. Patients with the latter received full dose LMWH for 1 week followed by half therapeutic dose LMWH for 3 weeks [10], while patients with unprovoked IDDVT received VKA for 12 weeks [11]. According to the preliminary report on a randomized trial showing that a short-term treatment with LMWH alone in therapeutic doses for two weeks, followed by half the dose for additional four weeks was an effective and safe alternative to warfarin in patients with IDDVT [12], patients with cancer received full dose LMWH for 2 weeks followed by half therapeutic dose LMWH for 4 weeks. All patients were instructed to wear 30-40 mmHg graduated compression knee high elastic stockings. Follow-up included visits at the outpatient clinic of our Unit, after one month, three months and after one year. All patients then received a phone call after two years. In case of worsening symptoms and/or suspected VTE the patients were seen in our outpatients service and underwent a whole leg ultrasonography, the results of which were compared with the previously available exam. Patients with symptoms of PE had diagnostic testing based on prestest clinical probability, D-dimer and multidetector CT scan. The end point of the present study was defined as the composite of PE, proximal DVT, and IDDVT recurrence/extension, cardiovascular death. Patients were censored when they reached the end-point or at the end of follow-up. All outcome events were adjudicated by two investigators (B.C, G.P) not involved in patient enrollment and follow-up and unaware of patient treatment.

The study was performed according to the recommendations of the Declaration of Helsinki and was approved by the local Ethics Committee. Written informed consent was obtained from all patients.

D-dimer

Blood samples for D-dimer testing were obtained before ultrasonography investigation as previously described [9]. Technicians performing D-dimer testing were unaware of the symptoms of the patients. The STA Liatest® D-dimer was performed on the STA Compact® coagulation analyzer and the cut-off value for DVT exclusion was 500 ng/mL [9].

Whole-leg Ultrasonography Investigation

At enrollment, at one and three months, patients underwent a comprehensive real-time B-mode and colour Doppler compression ultrasonography examination of both legs by a vascular medicine physician as previously described [9]. Ultrasonography investigation was carried out with an EnVisor C HD instrument (Philips Medical System S.p.A, Monza, Italy), with a high-resolution broadband width linear array transducer L 12-5 MHz, according to the complete or whole leg compression ultrasonography (C-CUS) with the method of Schellong [13]. C-CUS assesses proximal and distal veins in a single test and allows direct visualization (and diagnosis) of proximal DVT and IDDVT. The proximal deep veins were examined first, then the calf veins were evaluated. The following veins were scanned in the transverse plane over their entire length: posterior tibial veins, fibular veins, internal and external gastrocnemius veins, and soleal veins. The diagnosis of DVT was confirmed if there was lack of compression of the vein, combined with the absence of venous flow with distal compression and the visualization of intraluminal thrombus. The clot diameter at maximal compression and length were recorded at baseline and allowed to compare C-CUS during follow-up in case of new signs or symptoms. Results were recorded on a chart according to the location and extent of the clot.

IDDVT extension to proximal deep veins was defined as C-CUS-proven extension of IDDVT to the calf trifurcation, popliteal, femoral or iliac vein or new proximal DVT in the controlateral leg on a standardized C-CUS protocol performed by experienced vascular physician using the diagnostic criterion of vein incompressibility. The diagnosis of IDDVT rethrombosis was made when a) lack of compressibility of a previously compressible vein or b) an increase of at least 3 mm in the diameter of the residual thrombus during compression in a previously non compressible vein.

Statistical Analysis

Analysis was carried out using the SPSS software package (version 15.0; SPSS Inc. Chicago, Illinois, USA). Relationships between variables were assessed using Pearson correlation for continuous variables and chi-square or Fisher exact test for categorical variables. Student t-test was used to compare means among groups for normally distributed variables. Results are given as mean ± SEM. Cox's proportional hazard models were used to calculate hazard ratio for each variables. Cumulative end point curves were estimated with the Kaplan-Meier procedure, hazard ratios (HR) and their 95 percent confidence intervals (95% CI) were calculated with Cox's proportional hazard models. The associations between outcomes (a composite as indicated above) and risk factors for outcomes (age, sex, BMI, cancer, significantly reduced mobility, surgery, history of vein thrombosis, oestrogen-containing therapy, D-dimer, VKA treatment) were tested with univariable analysis followed by multivariable analysis. A parsimony model with predictors associated with a p-value < 0.1 was presented to improve precision and avoid over-fitting [14]. For Cox proportional hazard models a rule of thumb is to have at least 10 events per predictor variable to prevent overfitting. This is especially important in prediction because overfitting will lead to models that do not validate in other samples. Consequently, the results of predicting with an overfitted model are not generalizable to the general population. The significance level was set at <0.05.

Results

Characteristics of enrolled patients (n = 90) are summarized in Table 1. As previously described [8], the most frequent symptoms

Table 1
Characteristic of the study population.

Age, Mean ± SD (IQR):	61.0 ± 18.2 years (45.7-76.6)
Male/female (%):	44/46 (51.1)
BMI, Mean ± SD (IQR):	26.9 ± 5.6 kg m^{-2} (23.7-30.1)
Venous thromboembolism risk factors	
Active cancer:	8.9%
Surgery:	15.6%
Significantly reduced mobility:	34.4%
History of vein thrombosis:	15.6%
Obesity:	25.3%
Oestrogen-containing therapy:	8.9%
Symptoms	
Pain:	86.7%
Oedema:	62.9%
Redness or rash:	14.8%
Leg warmth:	12.8%